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(54) Title: LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING GINGIVITIS			
(57) Abstract  This invention provides methods for the treatment or inhibiting of gingivitis which comprises administering to a mammal in need thereof an effective amount of a compound having activity as a leukotriene B <sub>4</sub> antagonist.			

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## LEUKOTRIENE ANTAGONISTS USEFUL FOR TREATING GINGIVITIS

Gingivitis is defined as inflammation of the gingiva,  
5 characterized by swelling, redness, change of normal  
contours, watery exudate, and bleeding. Swelling deepens  
the crevice between the gingiva and the teeth, and gingival  
pockets form. Gingivitis is common and may be acute,  
chronic, or recurrent.

10 The most frequent single cause is poor hygiene,  
characterized by bacterial plaque (microbial colonies  
tenaciously attached to the tooth surfaces). Other local  
factors such as malocclusion, dental calculus (calcified  
plaque, called tartar), food impaction, faulty dental  
15 restorations, and mouth breathing play important secondary  
roles.

The outstanding signs of simple gingivitis are a band  
of red, inflamed gingiva along the necks of teeth, edematous  
swelling of the interdental papillae, and bleeding on  
20 minimal injury. Pain is usually absent. The inflammation,  
sometimes acute in onset, may subside, but without treatment  
it will persist in chronic form.

Uncontrolled diabetics have an exaggerated response to  
gingival irritants; secondary infections and acute gingival  
25 abscesses are common. Rapid, progressive periodontal bone  
loss is a common finding on x-ray examination.

Mild inflammation of the gingiva may develop in  
pregnancy; a similar gingivitis may accompany dysmenorrhea.

An engorged, edematous, painful, enlarged gingiva that  
30 bleeds readily suggests leukemia. This results from reduced  
tissue resistance, the presence of leukemic infiltrate in  
the periodontal tissue, and a characteristic bleeding  
abnormality. The gingiva may become secondarily infected  
with fusospirochetal organisms, resulting in acute  
35 necrotizing ulcerative gingivitis (ANUG).

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Drug induced gingivitis may occur upon treatment with phenytoin or cyclosporine. Calcium channel blockers in the presence of gingival inflammation may cause fibrotic gingival hyperplasia.

5       The gingiva in scurvy is inflamed, hyperplastic, engorged with blood, and bleeds easily. It may appear as "bags of blood." Petechial and ecchymotic areas may appear on the gingiva and elsewhere in the mouth. Destruction of periosteum and periodontal tissue, resulting in loosened  
10   teeth, is common. Gingival changes are not seen in edentulous patients. In pellagra, the gingiva is inflamed, bleeds easily, and is subject to secondary infection. The lips are reddened and cracked, the mouth feels scalded, the tongue is smooth and bright red, and tongue and mucosa may  
15   show ulcerations.

Recurrent episodes of acute inflammation of the gingival flap overlying a partially erupted tooth are common -- most often around the 3rd molar; extraction may be considered after the acute process subsides.

20       Gingival abscess (parulis) develops from a periapical abscess at the tip of the root of a nonvital tooth. Pus escapes from a sinus that opens on the mucosal surface. A periodontal abscess may drain similarly.

The treatment is to control or correct both plaque and  
25   local and systemic factors. Some cases require extensive treatment such as thorough scaling, replacement of overhanging fillings, and correction of poorly contoured restorations. Otherwise, microbial plaque is encouraged to accumulate along the gingival margins. Excision of excess  
30   gingiva may be required in specific situations as noted above. Acute stages respond to antibiotic therapy.

Research in the area of allergic reactions of the lung has provided evidence that arachidonic acid derivatives formed by the action of lipxygenases are related to various  
35   disease states. Some of these arachidonic acid metabolites have been classified as members of a family of eicosatetraenoic acids termed leukotrienes. Three of these

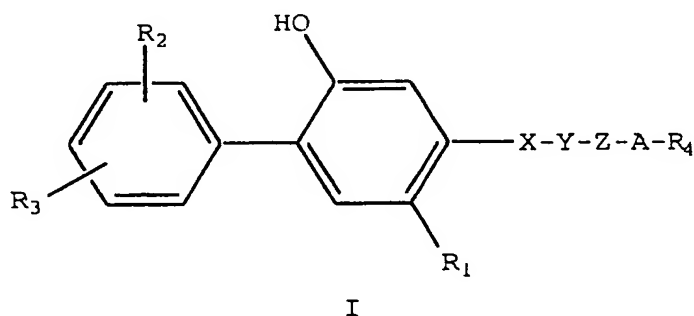
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substances are currently thought to be major components of what has been previously called slow reacting substance of anaphylaxis (SRS-A) and have been designated leukotrienes C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub> (LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>, respectively).

5 Another arachidonic acid metabolite, leukotriene B<sub>4</sub> (LTB<sub>4</sub>), is a proinflammatory lipid which has been implicated in the pathogenesis of psoriasis, arthritis, chronic lung diseases, acute respiratory distress syndrome, shock, asthma, inflammatory bowel diseases, and other inflammatory  
10 states characterized by the infiltration and activation of polymorphonuclear leukocytes and other proinflammatory cells. Polymorphonuclear leukocyte, when activated, liberated tissue-degrading enzymes and reactive chemicals causing the inflammation. Antagonism of LTB<sub>4</sub> should  
15 therefore provide a novel therapeutic approach to treatment of these and other LTB<sub>4</sub> mediated conditions.

Because of the debilitating effects of gingivitis and other inflammatory dental disorders, there continues to exist a need for effective treatments.

20 This invention provides a method for the treatment or inhibiting of gingivitis in mammals comprising administering to a mammal in need thereof an effective amount of a compound of Formula I



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wherein:

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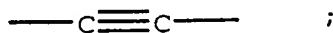
R<sub>1</sub> is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, (C<sub>1</sub>-C<sub>4</sub> alkyl)thio, halo, or R<sub>2</sub>-substituted phenyl;

5 each R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen, halo, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, (C<sub>1</sub>-C<sub>4</sub> alkyl)-S(O)<sub>q</sub>-, trifluoromethyl, or di-(C<sub>1</sub>-C<sub>3</sub> alkyl)amino;

10 X is -O-, -S-, -C(=O), or -CH<sub>2</sub>-;

Y is -O- or -CH<sub>2</sub>-;

15 or when taken together, -X-Y- is -CH=CH- or



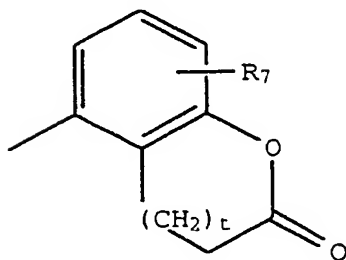
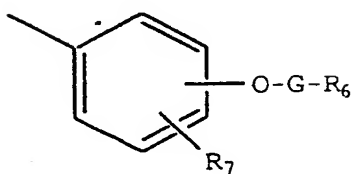
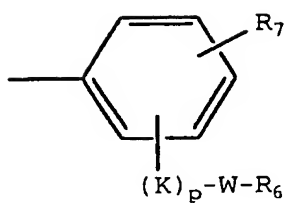
Z is a straight or branched chain C<sub>1</sub>-C<sub>10</sub> alkylidenyl;

20 A is a bond, -O-, -S-, -CH=CH-, or -CR<sub>a</sub>R<sub>b</sub>-, where R<sub>a</sub> and R<sub>b</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl, or R<sub>7</sub>-substituted phenyl, or when taken together with the carbon atom to which they are

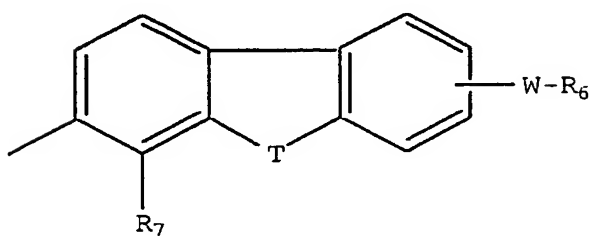
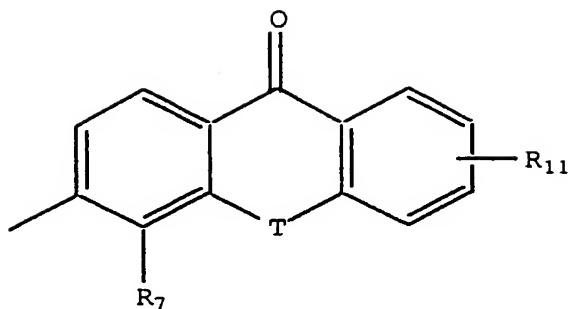
25 attached form a C<sub>4</sub>-C<sub>8</sub> cycloalkyl ring;

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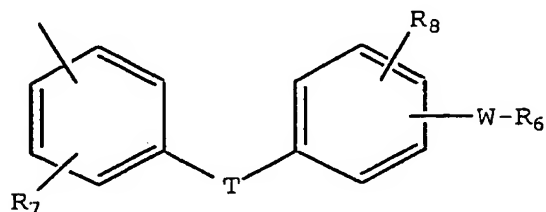
$R_4$  is  $R_6$



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or



where,

5

each R<sub>6</sub> is independently -COOH, 5-tetrazolyl, -CON(R<sub>9</sub>)<sub>2</sub>, or -CONHSO<sub>2</sub>R<sub>10</sub>;

10

each R<sub>7</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, benzyl, methoxy, -W-R<sub>6</sub>, -T-G-R<sub>6</sub>, (C<sub>1</sub>-C<sub>4</sub> alkyl)-T-(C<sub>1</sub>-C<sub>4</sub> alkylidenyl)-O-, or hydroxy;

R<sub>8</sub> is hydrogen or halo;



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each R<sub>9</sub> is independently hydrogen, phenyl, or C<sub>1</sub>-C<sub>4</sub> alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

5

R<sub>10</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl;

R<sub>11</sub> is R<sub>2</sub>, -W-R<sub>6</sub>, or -T-G-R<sub>6</sub>;

10

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

15

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH<sub>2</sub>-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)<sub>q</sub>-;

20

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

25

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

30

provided when A is -O- or -S-, R<sub>4</sub> is not R<sub>6</sub>;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

35

provided W is not a bond when p is 0;

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or a pharmaceutically acceptable salt or solvate thereof.

The following definitions refer to the various terms used throughout this disclosure.

The term "C<sub>1</sub>-C<sub>5</sub> alkyl" refers to the straight and  
5 branched aliphatic radicals of 1 to 5 carbon atoms such as methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, 2,2-dimethylpropyl, and the like. Included within this definition are the terms "C<sub>1</sub>-C<sub>3</sub> alkyl" and "C<sub>1</sub>-C<sub>4</sub> alkyl".

10 The term "C<sub>2</sub>-C<sub>5</sub> alkenyl" refers to straight and branched aliphatic radicals of 2 to 5 carbon atoms containing one double bond, such as -CH=CH<sub>2</sub>, -CH<sub>2</sub>CH=CH<sub>2</sub>, -CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>, -CH<sub>2</sub>C(CH<sub>3</sub>)=CH<sub>2</sub>, -CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>, and the like.

The term "C<sub>2</sub>-C<sub>5</sub> alkynyl" refers to straight and  
15 branched aliphatic residues of 2 to 5 carbon atoms containing one triple bond, such as -C≡CH, -CH<sub>2</sub>-C≡CH, -CH<sub>2</sub>CH<sub>2</sub>C≡CH, -CH<sub>2</sub>CH(CH<sub>3</sub>)C≡CH, -CH<sub>2</sub>C≡CCH<sub>3</sub>, and the like.

The term "C<sub>1</sub>-C<sub>4</sub> alkoxy" refers to methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, and tert-butoxy.

20 The term "halo" refers to fluoro, chloro, bromo, and iodo.

The term "C<sub>1</sub>-C<sub>10</sub> alkylidenyl" refers to a divalent radical derived from a C<sub>1</sub>-C<sub>10</sub> alkane such as -CH<sub>2</sub>-, -CH(CH<sub>3</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>-, -CH(C<sub>2</sub>H<sub>5</sub>)-, -CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)-,  
25 -CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH(CH<sub>3</sub>)-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>-, -CH<sub>2</sub>CH(C<sub>2</sub>H<sub>5</sub>)-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH(C<sub>2</sub>H<sub>5</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH(C<sub>2</sub>H<sub>5</sub>)-, -C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH(CH<sub>3</sub>)CH<sub>2</sub>CH(CH<sub>3</sub>)-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH(C<sub>2</sub>H<sub>5</sub>)CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-,  
30 -CH(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-, -(CH<sub>2</sub>)<sub>10</sub>-, and the like. Included within this definition are the terms "C<sub>1</sub>-C<sub>4</sub> alkylidene" and "C<sub>2</sub>-C<sub>4</sub> alkylidene".

The term "C<sub>4</sub>-C<sub>8</sub> cycloalkyl" refers to a cycloalkyl ring of four to eight carbon atoms, such as cyclobutyl,  
35 cyclopentyl, cyclohexyl, 4,4-dimethylcyclohexyl, cycloheptyl, cyclooctyl, and the like.

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The term "straight or branched chain divalent hydrocarbyl residue of one to eight carbon atoms" refers to a divalent radical derived from a straight or branched alkane, alkene, or alkyne of one to eight carbon atoms.

5 Depending upon the branching and number of carbon atoms, as will be appreciated by organic chemists, such a moiety can contain one, two or three double or triple bonds, or combinations of both. As such, this term can be considered an alkylidene group as defined above containing from 1 to 8  
10 carbon atoms optionally containing one to three double or triple bonds, or combinations of the two, limited as noted in the preceding sentence.

This invention includes the pharmaceutically acceptable base addition salts of the compounds of Formula  
15 I. Such salts include those derived from inorganic bases, such as ammonium and alkali and alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, as well as salts derived from basic organic amines, such as aliphatic and aromatic amines, aliphatic diamines, hydroxy  
20 alkylamines, and the like. Such bases useful in preparing the salts of this invention thus include ammonium hydroxide, potassium carbonate, sodium bicarbonate, calcium hydroxide, methyl amine, diethyl amine, ethylene diamine, cyclohexylamine, ethanolamine, and the like. The potassium  
25 and sodium salt forms are particularly preferred.

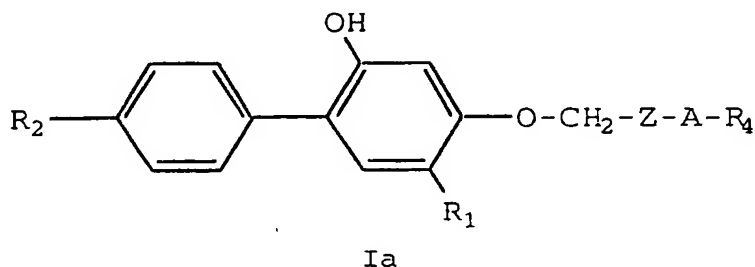
This invention includes both mono-salt forms, i.e., a 1:1 ratio of a compound of Formula I with a base as previously described, as well as di-salt forms in those instances where a compound of Formula I has two acidic  
30 groups. In addition, this invention includes any solvate forms of the compounds of Formula I or salts thereof, such as ethanol solvates, hydrates, and the like.

It is recognized that in compounds having branched alkyl, alkylidenyl, or hydrocarbyl functionality, and in  
35 those compounds bearing double or triple bonds, various stereoisomeric products may exist. This invention is not limited to any particular stereoisomer but includes all

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possible individual isomers and mixtures thereof. The term "5-tetrazolyl" refers to both tautomers, ie, (1H)-5-tetrazolyl and (2H)-5-tetrazolyl.

A most preferred group of compounds employed in the methods of the present invention are those compounds of Formula Ia:



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and pharmaceutically acceptable base addition salts thereof. Especially preferred are those compounds wherein R<sub>2</sub> is halo, particularly fluoro. Preferred R<sub>1</sub> substituents are propyl and especially ethyl.

15

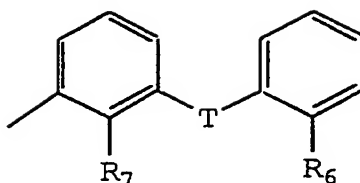
Preferred Z substituents include C<sub>2</sub>-C<sub>4</sub> alkylidene, particularly -CH<sub>2</sub>CH<sub>2</sub>- and -CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-. Preferred A groups include -O-, -CH<sub>2</sub>-, -CH(R<sub>7</sub>-substituted phenyl)-, and -C(CH<sub>3</sub>)<sub>2</sub>-.

Preferred R<sub>4</sub> groups include -COOH, 5-tetrazolyl, or a mono-, di-, or tri-cyclic group as drawn above wherein there is at least one acidic group attached to a ring, such as -W-COOH, -T-G-COOH, or the corresponding tetrazole derivatives. The preferred W moiety is that of a bond or straight chain C<sub>1</sub>-C<sub>4</sub> alkylidene; preferred G moieties are straight chain C<sub>1</sub>-C<sub>4</sub> alkylidene. It is preferred that R<sub>5</sub> or R<sub>7</sub> be C<sub>1</sub>-C<sub>4</sub> alkyl, especially n-propyl.

Particularly preferred groups are those wherein A is -CH(R<sub>7</sub>-substituted phenyl)- and R<sub>4</sub> is -COOH or 5-tetrazolyl. Also preferred are those compounds wherein A is -O- and R<sub>4</sub> is

30

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Preferred aspects of this substructure are those wherein R<sub>7</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, especially n-propyl, and R<sub>6</sub> is -  
5 W-COOH. Particularly preferred are those compounds wherein T  
is -O- or -S- and W is a bond.

Particularly preferred compounds of the instant invention include 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid;  
10 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propionic acid; 1-(4-(carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane; 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-9H-xanthene]]propanoic acid; 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenyl]-4-pentynoic acid or a pharmaceutically  
15 acceptable salt or solvate thereof.

20 The leukotriene B<sub>4</sub> (LTB<sub>4</sub>) antagonists employed in the methods of the present invention may be synthesized essentially as described in US Patent No. 5,462,954 issued October 31, 1995, the entire contents of which are herein incorporated by reference.

25 The following examples further illustrate the preparation of the intermediates and compounds employed in this invention. The examples are illustrative only and are not intended to limit the scope of the invention. Melting points were determined on a Thomas-Hoover apparatus and are  
30 uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. All chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. Chemical shifts

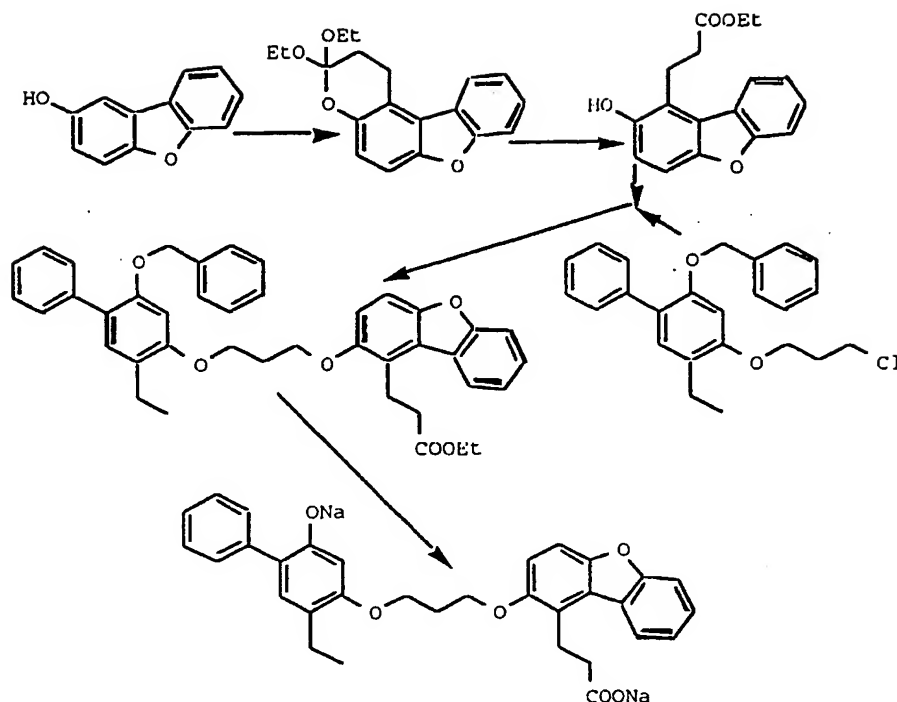
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of aromatic protons of quinoline species in DMSO-d<sub>6</sub> are concentration dependent. The following abbreviations are used to denote signal patterns: s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet. Infrared spectra were determined on a Nicolet DX10 FT-IR spectrometer. Mass spectral data were determined on a CEC-21-110 spectrometer using electron impact (EI) conditions, a MAT-731 spectrometer using free desorption (FD) conditions, or a VG ZAB-3F spectrometer using fast atom bombardment (FAB) conditions. Silica gel chromatography was performed using ethyl acetate/hexane gradients unless otherwise indicated. Reverse-phase chromatography was performed on MCI CHP20P gel using an acetonitrile/water or methanol/water gradient unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. All reactions were conducted under argon atmosphere with stirring unless otherwise noted. Where structures were confirmed by infra-red, proton nuclear magnetic resonance, or mass spectral analysis, the compound is so designated by "IR", "NMR", or "MS", respectively.

#### Example 1

3-[2-[3-[(5-Ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt

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A. Preparation of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran.

5

A solution of 2-hydroxydibenzofuran (5.00 g, 27.2 mmol), triethylorthoacrylate (10.1 g, 54.3 mmol) and pivalic acid (1.39 g, 13.6 mmol) in toluene (100 mL) was refluxed for 18 hours. The mixture was cooled to room temperature and washed once with water and once with a saturated sodium bicarbonate solution, dried over sodium sulfate, filtered and concentrated in vacuo to provide an orange oil. This material was diluted with hexane and maintained at -20°C for 18 hours. The resulting crystals were collected via vacuum filtration to provide 5.67 g (67%) of the desired title intermediate, mp 64°C; NMR (CDCl<sub>3</sub>) 7.96 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8 Hz, 1H), 7.35 (m, 2H), 7.06 (d, J = 8.8 Hz, 1H), 3.82 (q, J = 7.2 Hz, 2H), 3.73 (q, J = 6.8 Hz, 2H), 3.35 (t, J = 6.9 Hz, 2H), 2.29 (t, J = 7.0 Hz, 2H), 1.23 (t, J = 7.1 Hz, 6H); MS-FD m/e 312

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(p); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2982, 1494, 1476, 1451, 1434, 1251, 1090, 1054, 975.

Analysis for C<sub>19</sub>H<sub>20</sub>O<sub>4</sub>:

Calc: C, 73.06; H, 6.45;  
5 Found: C, 72.81; H, 6.72.

B. Preparation of 3-[1-(2-hydroxydibenzofuran)]-propanoic acid ethyl ester.

10 A mixture of 3,3-diethoxy-2,3-dihydro-1H-benzofuro-[3,2-f][1]benzopyran (3.50 g, 11.2 mmol) and 10% aqueous hydrochloric acid (5 mL) in ethyl acetate (30 mL) was stirred at room temperature for 1 hour. The resulting mixture was washed once with water, dried over sodium sulfate, filtered  
15 and concentrated *in vacuo* to provide a tan solid. Recrystallization from hexane/ethyl acetate provided 3.11 g (98%) of the desired title intermediate as an off-white crystalline material: mp 128-131°C; NMR (CDCl<sub>3</sub>) 7.88 (d, J = 7.7 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 7.2 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.36 (t, J = 6.6 Hz, 1H), 7.13  
20 (d, J = 8.8 Hz, 1H), 7.13 (q, J = 8.8 Hz, 2H), 3.43 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 7.7 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H); MS-FD m/e 284 (100, p), 256 (65), 238 (17); IR (KBr, cm<sup>-1</sup>) 2985 (b), 1701, 1430, 1226, 1183, 1080.

25 Analysis for C<sub>17</sub>H<sub>16</sub>O<sub>4</sub>:

Calc: C, 71.82; H, 5.67;  
Found: C, 71.90; H, 5.43.

C. Preparation of 3-[2-[3-[[5-ethyl-2-(phenylmethoxy)-[1,1'-biphenyl]-4-yl]oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester.

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3-[1-(2-Hydroxydibenzofuran)]propanoic acid ethyl ester (625 mg, 2.20 mmol) was dissolved in dimethylformamide (10 mL) and carefully treated at room temperature with 95% sodium hydride (58 mg, 2.4 mmol). When gas evolution had  
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ceased, 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (836 mg, 2.20 mmol) was added and the resulting mixture was stirred for 18 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide a dark oil. Silica gel chromatography (ethyl acetate/hexane) provided 200 mg (14%) of the desired titled intermediate as a colorless oil: NMR (CDCl<sub>3</sub>) 8.11 (d, J = 7.7 Hz, 1H), 7.57 (m, 3H), 7.48 (t, J = 7.3 Hz, 1H), 7.20-7.44 (m, 10 H), 7.17 (s, 1H), 7.08 (d, J = 8.9 Hz, 1H), 6.67 (s, 1H), 5.05 (s, 2H), 4.29 (t, J = 6.2 Hz, 2H), 4.26 (t, J = 6.1 Hz, 2H), 4.15 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 8.5 Hz, 2H), 2.67 (m, 4H), 2.37 (t, J = 6.0 Hz, 2H), 1.21 (m, 6H).

15

D. Preparation of 3-[2-[3-[(5-ethyl-2-hydroxy[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid disodium salt.

20 To a nitrogen-purged solution of 3-[2-[3-[(5-ethyl-2-(phenylmethoxy)[1,1'-biphenyl]-4-yl)oxy]propoxy]-1-dibenzofuran]propanoic acid ethyl ester (200 mg, 0.318 mmol) in a 1:1 mixture of methanol/tetrahydrofuran (40 mL) was added 10% palladium on carbon (25 mg). The resulting suspension was hydrogenated at 1 atm pressure for 24 hours at room temperature. The mixture was filtered through a short pad of Florisil® and the filtrate concentrated in vacuo. The residue was dissolved in a 1:1 mixture of methanol/tetrahydrofuran (20 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 24 hours. The resulting mixture was extracted once with diethyl ether. The aqueous layer was acidified with 5N hydrochloric acid solution and extracted twice with methylene chloride. The combined methylene chloride fractions were concentrated in vacuo. The residue was dissolved in a minimum of 1N sodium hydroxide solution and purified on HP-20 resin to provide 53 mg (30%) of the desired title product as a fluffy white

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solid: NMR (DMSO-d<sub>6</sub>) 8.12 (d, J = 6.9 Hz, 1H), 7.64 (d, J = 8.2 Hz, 1H), 7.37-7.57 (m, 5H), 7.30 (m, 2H), 7.14 (m, 2H), 6.96 (s, 1H), 6.93 (s, 1H), 4.30 (t, J = 7.3 Hz, 2H), 4.14 (t, J = 5.4 Hz, 2H), 2.48 (m, 4H), 2.23 (m, 4H), 1.10 (t, J = 7.6 Hz, 3H); MS-FAB m/e 555 (88, p + 1), 533 (62); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 3384 (b), 2969, 1566, 1428, 1257, 1181.

Analysis for C<sub>32</sub>H<sub>28</sub>O<sub>6</sub>Na<sub>2</sub>:

Calc: C, 69.31; H, 5.09;

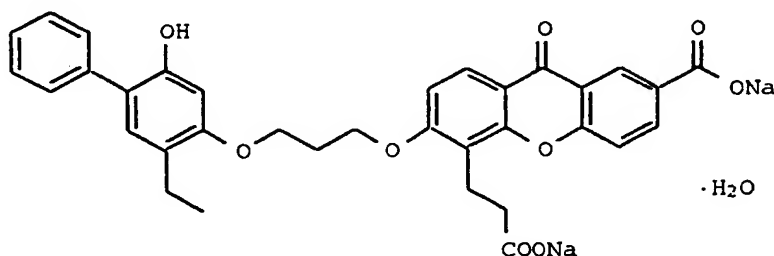
Found: C, 69.51; H, 5.39.

10

### Example 2

7-Carboxy-9-oxo-3-[3-(2-ethyl-5-hydroxy-4-phenylphenoxy)propoxy]-9H-xanthene-4-propanoic acid disodium salt monohydrate

15



A mixture of 2-benzyloxy-1-phenyl-5-ethyl-4-(3-chloro-1-propyloxy)benzene (749 mg, 1.97 mmol), ethyl 7-carboethoxy-3-hydroxy-9-oxo-9H-xanthene-4-propanoate (729 mg, 1.97 mmol), potassium carbonate (1.36 g, 9.85 mmol) and potassium iodide (33 mg, 0.20 mmol) was refluxed for 24 hours. Dimethylsulfoxide (2 mL) was added and heating continued for 24 hours. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed once with water. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to reveal a tan solid. This material was dissolved in ethyl acetate (30 mL) and the resulting solution purged with nitrogen. To this solution was added 10% palladium on carbon (120 mg) and the

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resulting suspension hydrogenated at 1 atmosphere of pressure. The solution was filtered and concentrated in vacuo to provide a colorless oil. This material was dissolved in a solution of 1:1 methanol/tetrahydrofuran (30 mL) and treated with 5N sodium hydroxide solution (2 mL) at room temperature for 18 hours. The resulting solution was extracted once with diethyl ether and the aqueous layer acidified with 5N hydrochloric acid solution. The resulting precipitate was collected via suction filtration. This material was converted to the di-sodium salt and purified as described above for the preparation of Example 1(D) to provide 390 mg (56%) of the desired title product as a fluffy white solid: NMR (DMSO-d<sub>6</sub>) 12.65 (s, 1H, -OH), 8.65 (s, 1H), 8.28 (dd, J = 8.5, 2.0 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.50 (m, 3H), 7.29 (t, J = 7.8 Hz, 2H), 7.17 (m, 2H), 6.93 (s, 1H), 6.89 (s, 1H), 4.26 (m, 4H), 3.12 (m, 2H), 2.47 (m, 2H), 2.23 (m, 2H), 1.10 (t, J = 7.4 Hz, 3H); MS-FAB m/e 627 (24, p), 605 (40), 583 (24), 331 (24), 309 (100); IR (KBr, cm<sup>-1</sup>) 3419 (b), 2962, 1612, 1558, 1443, 1390, 1277, 1084.

Analysis for C<sub>34</sub>H<sub>28</sub>O<sub>9</sub>Na<sub>2</sub>·H<sub>2</sub>O:

Calc: C, 63.34; H, 4.69;

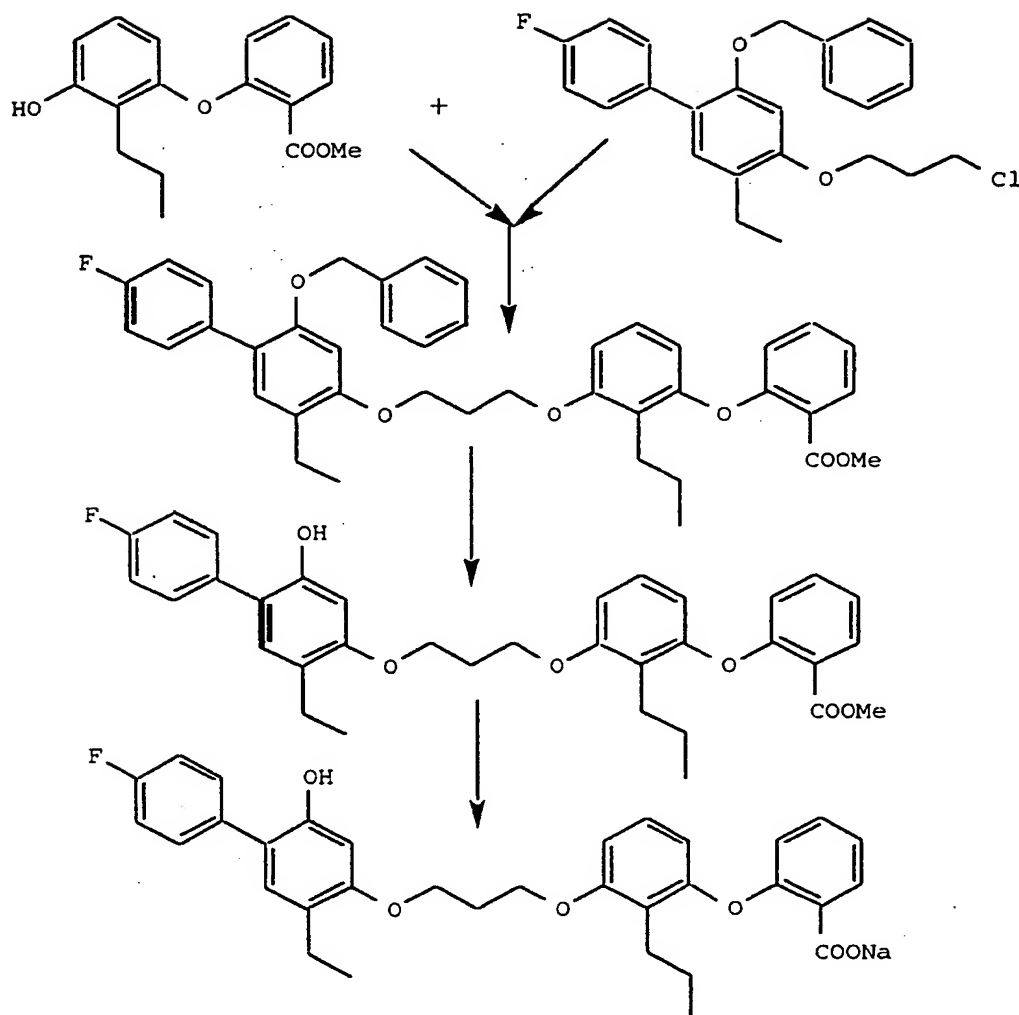
Found: C, 63.36; H, 4.50.

25

Example 3

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt

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A. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-(phenylmethoxy)phenoxy]propoxy]phenoxy]-  
 5 benzoic acid methyl ester.

A mixture of 2-benzyloxy-1-(4-fluorophenyl)-5-ethyl-4-(3-chloro-1-propyloxy)benzene (20.0 g, 50.2 mmol) and sodium iodide (75.3 g, 502 mmol) in 2-butanone (200 mL) was  
 10 refluxed for 6 hours. The mixture was diluted with ether and washed once with water. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to provide a colorless oil. This material was dissolved in

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dimethylformamide (100 mL) and treated with 2-(3-hydroxy-2-propylphenoxy)benzoic acid methyl ester (14.4 g, 50.2 mmol) and potassium carbonate (20.8 g, 151 mmol) at room temperature for 24 hours. This mixture was diluted with  
5 water and twice extracted with ether. The aqueous layer was separated and back-extracted once with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to provide a yellow oil. Silica gel chromatography provided 25.4 g (78%) of the  
10 desired title intermediate as a pale golden oil: NMR (CDCl<sub>3</sub>) 7.91 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.25-7.43 (m, 6H), 7.03-7.38 (m, 5H), 6.84 (d, J = 8.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.63 (s, 1H), 6.47 (d, J = 8.1 Hz, 1H), 5.03 (s, 2H), 4.24  
15 (t, J = 5.7 Hz, 2H), 4.21 (t, J = 5.8 Hz, 2H), 3.86 (s, 3H), 2.69 (t, J = 7.8 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 2.34 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 5.0 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H), 0.94 (t, J = 7.5 Hz, 3H); MS-FD m/e 648 (p); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2960, 1740, 1604, 1497, 1461,  
20 1112.

Analysis for C<sub>41</sub>H<sub>41</sub>O<sub>6</sub>F:

Calc: C, 75.91; H, 6.37;

Found: C, 76.15; H, 6.45.

25 B. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-  
30 (phenylmethoxy)phenoxy]propoxy]phenoxy]benzoic acid methyl ester (33.0 g, 50.9 mmol) was de-benzylated as described above for the preparation of Example 2 to provide 27.3 g (96%) of the title intermediate as an amber oil: NMR (CDCl<sub>3</sub>) 7.90 (dd, J = 7.8, 1.7 Hz, 1H), 7.42 (m, 3H), 7.05-  
35 7.23 (m, 4H), 6.99 (s, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.70 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H), 6.46 (d, J = 8.1 Hz, 1H),

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5.05 (s, 1H, -OH), 4.23 (m, 4H), 3.86 (s, 3H), 2.68 (t, J = 7.4 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 2.36 (quintet, J = 6.0 Hz, 2H), 1.60 (hextet, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); MS-FD m/e 558 (p); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 2965, 1727, 1603, 1496, 1458, 1306, 1112.

Analysis for C<sub>34</sub>H<sub>35</sub>O<sub>6</sub>F:

Calc: C, 73.10; H, 6.31;

Found: C, 73.17; H, 6.42.

- 10 C. Preparation of 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid sodium salt.

2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid methyl ester (21.5 g, 38.5 mmol) was hydrolyzed as described above for the preparation of Example 2. The acid was converted to the sodium salt and purified as described above for the preparation of Example 1(D) to provide 16.7 g (77%) of the desired title product as a white amorphous solid: NMR (DMSO-d<sub>6</sub>) 10.50 (bs, 1H, -OH), 7.51 (m, 3H), 7.20 (t, J = 7.4 Hz, 1H), 7.13 (m, 2H), 7.00 (m, 2H), 6.95 (s, 1H), 6.67 (dd, J = 8.2, 3.3 Hz, 2H), 6.62 (s, 1H), 6.26 (d, J = 8.2 Hz, 1H), 4.14 (t, J = 5.8 Hz, 2H), 4.02 (t, J = 5.7 Hz, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.47 (q, J = 7.3 Hz, 2H), 2.16 (t, J = 5.9 Hz, 2H), 1.45 (hextet, J = 7.5 Hz, 2H), 1.07 (t, J = 7.5 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS-FAB m/e 568 (38, p + 1), 567 (100, p), 544 (86), 527 (77), 295 (65), 253 (45); IR (KBr, cm<sup>-1</sup>) 3407 (b), 2962, 1603, 1502, 1446, 1395, 1239, 1112.

Analysis for C<sub>33</sub>H<sub>32</sub>O<sub>6</sub>FNa:

Calc: C, 69.95; H, 5.69; F, 3.35;

Found: C, 69.97; H, 5.99; F, 3.52.

- 35 The methods of the present invention describe the use of leukotriene antagonists for the treatment or

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inhibition of gingivitis which is characterized by the excessive release of leukotriene B<sub>4</sub>.

The term "excessive release" of a leukotriene refers to an amount of the leukotriene sufficient to cause the symptoms of gingivitis. The amount of leukotriene which is considered to be excessive will depend on a variety of factors, including the amount of leukotriene required to cause the disease, and the species of the mammal involved. As will be appreciated by those skilled in the art, the success of treating a mammal suffering from or susceptible to gingivitis characterized by an excessive release of leukotriene with a compound of Formula I will be measured by the regression or prevention of the symptoms of the condition.

#### Assays

##### Assay 1

The effectiveness of compounds of Formula I to inhibit the binding of tritiated LTB<sub>4</sub> to guinea pig lung membranes was determined as follows.

#### [<sup>3</sup>H]-LTB<sub>4</sub> Radioligand Binding Assay in Guinea Pig Lung Membranes

[<sup>3</sup>H]-LTB<sub>4</sub> (196-200 Ci/mmol) was purchased from New England Nuclear (Boston, MA). All other materials were purchased from Sigma (St. Louis, MO). Incubations (555 mL) were performed in polypropylene minitubes for 45 minutes at 30°C and contained 25 mg of guinea pig lung membrane protein (Silbaugh, *et al.*, European Journal of Pharmacology, 223 (1992) 57-64) in a buffer containing 25 mM MOPS, 10 mM MgCl<sub>2</sub>, 10 mM CaCl<sub>2</sub>, pH 6.5, approximately 140 pM [<sup>3</sup>H]-LTB<sub>4</sub>, and displacing ligand or vehicle (0.1% DMSO in 1 mM sodium carbonate, final concentration) as appropriate. The binding reaction was terminated by the addition of 1 mL ice cold wash buffer (25 mM Tris-HCl, pH 7.5) followed immediately by vacuum filtration over Whatman GF/C glass fiber filters

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using a Brandel (Gaithersburg, MD) 48 place harvester. The filters were washed three times with 1 mL of wash buffer. Retained radioactivity was determined by liquid scintillation counting at 50% counting efficiency using Ready Protein Plus cocktail (Beckman, Fullerton, CA). Nondisplaceable binding was determined in the presence of 1 mM LTB<sub>4</sub> and was usually less than 10% of total binding. Data were analyzed using linear regression analysis of log-logit plots of the values between 10% and 90% of control binding to calculate IC<sub>50</sub>s and slope factors (pseudo-Hill coefficients). IC<sub>50</sub> values thus obtained were corrected for radioligand concentration (Cheng and Prusoff, Biochem. Pharmacol., 22, 3099 (1973)) to calculate K<sub>i</sub> values. pK<sub>i</sub> is the mean -log K<sub>i</sub> for n experiments.

Compounds of the instant invention tested in the above assay were found to have a pK<sub>i</sub> of between 7 and 11.

The ability of a compound of formula I to effectively treat experimental inflammation in the oral cavity can be evaluated in two models, ligature-induced periodontitis in monkeys (Smith, et al., Infect. Immun., 61, 1453-9, 1993) and naturally-occurring gingivitis in SUS rats (Isogai, et al., J. Periodontal., 65, 710-2, 1994).

#### Assay 2

For the monkey model, eight teeth on the right side of the mouth are ligated at the cemento-enamel junction with 3-0 silk. Animals are examined every 2 weeks for 6 months. On examination day, animals are anesthetized and three sites on each tooth, mesiobuccal, buccal and distobuccal, studied.

Gingival erythema is scored on a scale of 0 to 4 for none, mild, moderate and severe disease, respectively. Severest lesions are those with ulceration and necrosis. Bleeding, if it occurs on probing the tooth pocket with a controlled-force Florida probe, is recorded. Pocket depths and cemento-enamel junction levels are determined to the nearest 0.1 mm with the Florida probe, using the pocket



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measuring handpiece to enable Ramfjord attachment level calculations to be made.

Measurements of bone loss are made by obtaining standardized radiographs just before applying the ligatures and again at 3 and 6 months after their installation. The radiographs are digitized with the aid of a video camera coupled to an analog-to-digital converter and analyzed blindly. The distance between the cemento-enamel junction and the crest of the alveolar bone is determined for mesial and distal root surfaces.

Dose-response effects are obtained by dividing the animals into 4 experimental groups, each containing 5 monkeys, and dosing daily by gavage with either vehicle, or 10, 25, or 50 mg/kg of a compound of formula I. The effectiveness of a treatment is assessed by comparing the gingival erythema scores, bleeding sites, change in attachment level, and bone loss of the treated groups to that of the placebo control.

### 20 Assay 3

For naturally-occurring gingivitis studies, SUS rats are treated with either vehicle or a compound of formula I for 4 months. The animals are sacrificed at the end of this period and the degree of plaque accumulation and gingivitis measured.

Plaque formation is scored as follows: zero for no plaque accumulation; 1 for slight plaque accumulation and pocket formation (<1 mm); 2 for moderate plaque accumulation and pocket formation (1 to 3 mm); and 3 for severe plaque accumulation and deep pocket formation (>3 mm). The index for gingival inflammation is: zero for absence of inflammation; 1 for mild inflammation with slight change to reddish color and little swelling; 2 for moderate inflammation with change in reddish color, obvious swelling and the appearance of abrasions or bleeding on pressure; and 3 for severe inflammation with change in reddish color, pronounced swelling and spontaneous bleeding.

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Dose-response effects are obtained by dividing the animals into 4 experimental groups of 15 each. The groups are dosed daily by gavage with either vehicle, or 10, 25, or 50 mg/kg of a compound of formula I. The effectiveness of a treatment is assessed by comparing the plaque accumulation score and gingival inflammation index of the treated groups to that of the placebo control.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, that is effective to inhibit or treat gingivitis.

The term "inhibit" includes its generally accepted meaning which includes prohibiting, preventing, restraining and slowing, stopping or reversing progression, severity or a resultant symptom. As such, the present method includes both medical therapeutic and/or prophylactic administration as appropriate.

While it is possible to administer a compound employed in the methods of this invention directly without any formulation, the compounds are usually administered in the form of pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the present invention. The compounds or formulations of the present invention may be administered by the oral and rectal routes, topically, parenterally, e.g., by injection and by continuous or discontinuous intra-arterial infusion, in the form of, for example, tablets, lozenges, sublingual tablets, sachets, cachets, elixirs, gels, suspensions, aerosols, ointments, for example, containing from 0.01 to 90% by weight of the active compound in a suitable base, soft and hard gelatin capsules, suppositories, injectable solutions and suspensions in physiologically acceptable media, and sterile packaged powders adsorbed onto a support material for making injectable solutions. Such formulations are prepared in a manner well known in the pharmaceutical art and comprise at

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least one active compound. See, e.g., REMINGTON'S  
PHARMACEUTICAL SCIENCES, (16th ed. 1980).

In making the formulations employed in the present invention the active ingredient is usually mixed with an  
5 excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active  
10 ingredient. In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of  
15 less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable carriers, excipients and  
20 diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, water, syrup, and methyl cellulose.  
25 The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxybenzoates; sweetening agents; and flavoring  
30 agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compounds of this invention may be delivered  
35 transdermally using known transdermal delivery systems and excipients. Most preferably, a compound of this invention is admixed with permeation enhancers including, but not

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limited to, propylene glycol, polyethylene glycol monolaurate, and azacycloalkan-2-ones, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers, and buffers may be added to the transdermal formulation as desired.

For topical administration, a compound of this invention ideally can be admixed with any variety of excipients in order to form a viscous liquid or cream-like preparation.

For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

In the case of tablets, a lubricant may be incorporated to prevent sticking and binding of the powdered ingredients in the dies and on the punch of the tableting machine. For such purpose there may be employed for instance aluminum, magnesium or calcium stearates, talc or mineral oil.

Preferred pharmaceutical forms of the present invention include capsules, tablets suspensions and gels.

The therapeutic and prophylactic treatments provided by this invention are practiced by administering to a mammal in need thereof a dose of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof that is effective to inhibit or treat gingivitis.

Advantageously for this purpose, formulations may be provided in unit dosage form, preferably each dosage unit containing from about 5 to about 500 mg (from about 5 to 50 mg in the case of parenteral or inhalation administration, and from about 25 to 500 mg in the case of oral or rectal administration) of a compound of Formula I. Dosages from about 0.5 to about 300 mg/kg per day, preferably 0.5 to 20 mg/kg, of active ingredient may be administered although it will, of course, readily be understood that the amount of the compound or compounds of Formula I actually to be administered will be determined by a physician, in the light of all the relevant circumstances including the condition to be treated, the choice of compound to be administered and

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the choice of route of administration and therefore the above preferred dosage range is not intended to limit the scope of the present invention in any way.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the route of administration the age, weight and response of the individual patient, the condition being treated and the severity of the patient's symptoms.

In general, the compounds of the invention are most desirably administered at a concentration that will generally afford effective results without causing any serious side effects and can be administered either as a single unit dose, or if desired, the dosage may be divided into convenient subunits administered at suitable times throughout the day.

While all of the compounds illustrated above exemplify LTB<sub>4</sub> inhibition activity in vitro, we have also discovered that compounds bearing a single acidic group (R<sub>6</sub>) are considerably more orally bioactive when administered to mammals compared with those compounds bearing two such acidic groups. Thus, a preferred embodiment when administering compounds of Formula I orally to mammals comprises administering compounds bearing a single acidic R<sub>6</sub> functionality.

The following formulation examples may employ as active compounds any of the compounds of this invention. The examples are illustrative only and are not intended to limit the scope of the invention in any way.

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Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

5

Quantity (mg/capsule)

10	3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propanoic acid	250
	Starch	200
	Magnesium stearate	10

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

15

Formulation 2

A tablet is prepared using the ingredients below:

20

Quantity (mg/tablet)

25	1-(4-(Carboxymethoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane	250
	Cellulose, microcrystalline	400
	Silicon dioxide, fumed	10
	Magnesium stearate	5

The components are blended and compressed to form tablets each weighing 665 mg.

30

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Formulation 3

An aerosol solution is prepared containing the following components:

5		<u>Weight %</u>
	3-[4-[7-Carboxy-9-oxo-3-[3-[2-ethyl-4-	
	(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-	
10	9H-xanthene]]propanoic acid	0.25
	Ethanol	30.00
	Propellant 11	10.25
	(trichlorofluoromethane)	
	Propellant 12	29.75
15	(Dichlorodifluoromethane)	
	Propellant 114	29.75
	(Dichlorotetrafluoroethane)	

The active compound is dissolved in the ethanol and the solution is added to the propellant 11, cooled to -30°C. and transferred to a filling device. The required amount is then fed to a container and further filled with the pre-mixed propellants 12 and 114 by means of the cold-filled method or pressure-filled method. The valve units are then fitted to the container.

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Formulation 4

Tablets each containing 60 mg of active ingredient are made up as follows:

5

	2-[2-Propyl-3-[3-[2-ethyl-5-hydroxy-4-(4-fluorophenyl)phenoxy]propoxy]phenoxy]-benzoic acid sodium salt	60 mg
10	Starch	45 mg
	Microcrystalline cellulose	35 mg
	Polyvinylpyrrolidone (as 10% solution in water)	4 mg
	Sodium carboxymethyl starch	4.5 mg
15	Magnesium stearate	0.5 mg
	Talc	1 mg
	Total	150 mg

20 The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50-60° and passed through a No. 18 mesh U.S. sieve. The sodium  
25 carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.



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Formulation 5

Capsules each containing 80 mg of medicament are made as follows:

5	5-[3-[2-(1-Carboxy)ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]-phenyl]-4-pentynoic acid	80 mg
	Starch	59 mg
10	Microcrystalline cellulose	59 mg
	Magnesium stearate	2 mg
	Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories each containing 225 mg of active ingredient are made as follows:

25	3-(2-(3-(2-Ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxyphenoxy)phenyl)propanoic acid	250
	Starch	200
	Magnesium stearate	10

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

35

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Formulation 7

Suspensions each containing 50 mg of medicament per 5 mL dose are made as follows:

5	2-[2-Propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	50 mg
	Sodium carboxymethyl cellulose	50 mg
10	Sugar	1 g
	Methyl paraben	0.05 mg
	Propyl paraben	0.03 mg
	Flavor	q.v.
	Color	q.v.
15	Purified water to	5 mL

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose, sugar, and a portion of the water to form a suspension. The parabens, flavor and color are dissolved and diluted with some of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

25 An intravenous formulation may be prepared as follows:

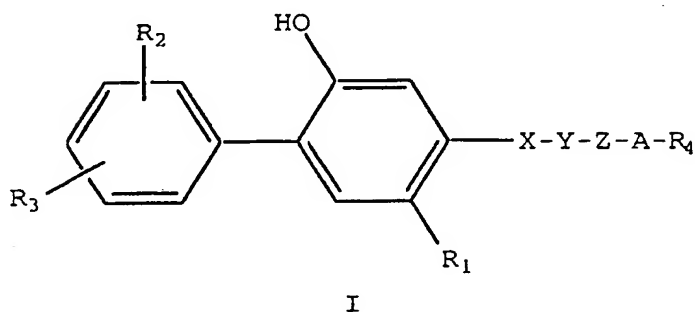
2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid	100 mg
Isotonic saline	1,000 ml

30 The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

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We claim:

1. A method for treating or inhibiting  
 5 gingivitis in a mammal which comprises administering to a  
 mammal in need thereof an effective amount of a compound of  
 the formula I



wherein:

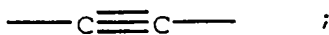
R<sub>1</sub> is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl,  
 15 C<sub>1</sub>-C<sub>4</sub> alkoxy, (C<sub>1</sub>-C<sub>4</sub> alkyl)thio, halo, or R<sub>2</sub>-  
 substituted phenyl;

each R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen,  
 20 halo, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, (C<sub>1</sub>-C<sub>4</sub>  
 alkyl)-S(O)<sub>q</sub>-, trifluoromethyl, or di-(C<sub>1</sub>-C<sub>3</sub>  
 alkyl)amino;

X is -O-, -S-, -C(=O), or -CH<sub>2</sub>-;

25 Y is -O- or -CH<sub>2</sub>-;

or when taken together, -X-Y- is -CH=CH- or



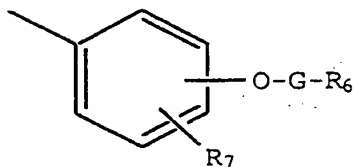
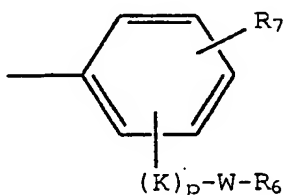
-34-

Z is a straight or branched chain C<sub>1</sub>-C<sub>10</sub> alkylidenyl;

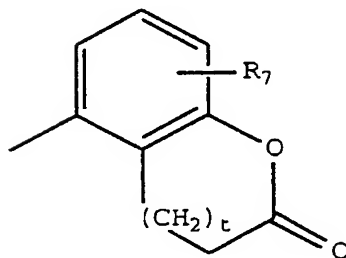
5

A is a bond, -O-, -S-, -CH=CH-, or -CR<sub>a</sub>R<sub>b</sub>-, where R<sub>a</sub> and R<sub>b</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl, or R<sub>7</sub>-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C<sub>4</sub>-C<sub>8</sub> cycloalkyl ring;

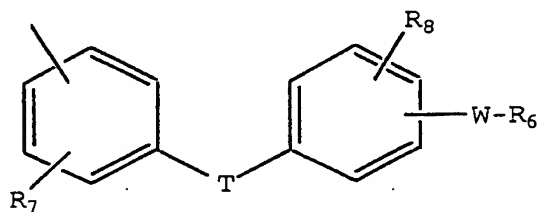
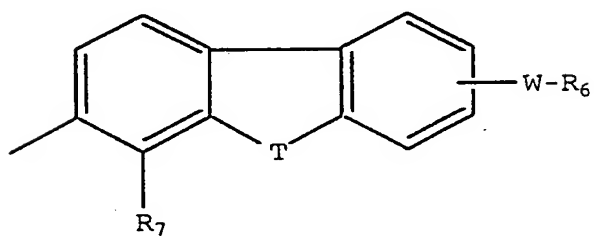
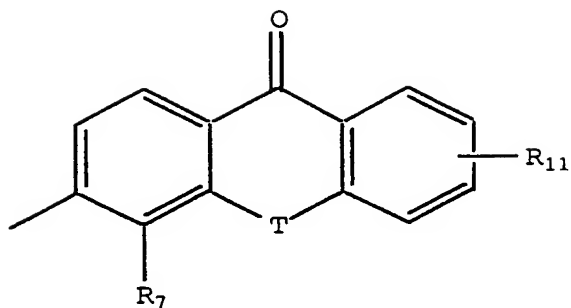
R<sub>4</sub> is R<sub>6</sub> ,



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-35-



where,

5

each R<sub>6</sub> is independently -COOH, 5-tetrazolyl, -CON(R<sub>9</sub>)<sub>2</sub>, or -CONHSO<sub>2</sub>R<sub>10</sub>;

10

each R<sub>7</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, benzyl, methoxy, -W-R<sub>6</sub>, -T-G-R<sub>6</sub>, (C<sub>1</sub>-C<sub>4</sub> alkyl)-T-(C<sub>1</sub>-C<sub>4</sub> alkylidenyl)-O-, or hydroxy;

R<sub>8</sub> is hydrogen or halo;

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each R<sub>9</sub> is independently hydrogen, phenyl, or C<sub>1</sub>-C<sub>4</sub> alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

5

R<sub>10</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl;

R<sub>11</sub> is R<sub>2</sub>, -W-R<sub>6</sub>, or -T-G-R<sub>6</sub>;

10

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

15

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH<sub>2</sub>-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)<sub>q</sub>-;

20

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

25

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

30

provided when A is -O- or -S-, R<sub>4</sub> is not R<sub>6</sub>;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

35

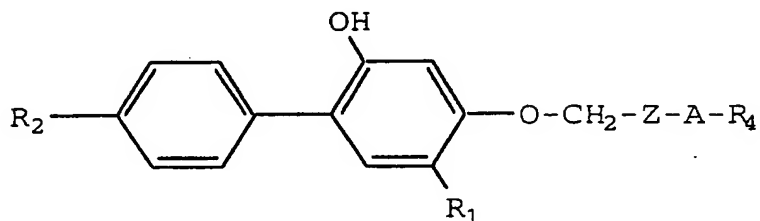
provided W is not a bond when p is 0;

-37-

or a pharmaceutically acceptable salt or solvate thereof.

2. The method as claimed in **Claim 1** employing a compound of the formula

5



or a pharmaceutically acceptable salt or solvate thereof.

10 3. The method as claimed in **Claim 2** employing 2-[2-propyl-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid or a pharmaceutically acceptable salt or solvate thereof.

15 4. The method as claimed in **Claim 2** employing 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)propoxy)-6-(4-carboxy-phenoxy)phenyl)propionic acid or a pharmaceutically acceptable salt or solvate thereof.

20 5. The method as claimed in **Claim 2** employing 1-(4-(carboxy-methoxy)phenyl)-1-(1H-tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy)hexane or a pharmaceutically acceptable salt or solvate thereof.

25 6. The method as claimed in **Claim 2** employing 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid or a pharmaceutically acceptable salt or solvate thereof.

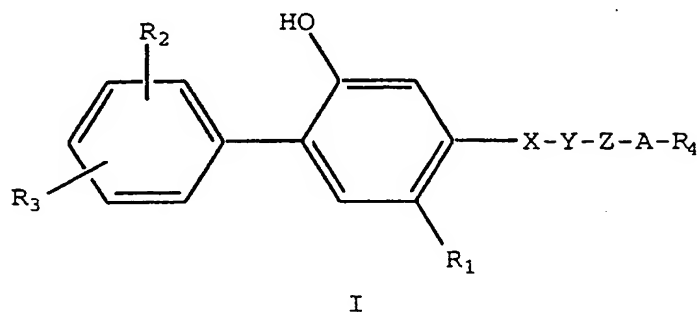
30 7. The method as claimed in **Claim 2** employing 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-

-38-

hydroxyphenoxy]-propoxy]phenyl]-4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

8. The method as claimed in any one of **Claims 1**  
5 **to 7** in which the mammal is a human.

9. Use of a compound of formula I;



wherein:

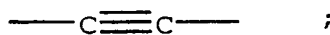
R<sub>1</sub> is C<sub>1</sub>-C<sub>5</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl,  
15 C<sub>1</sub>-C<sub>4</sub> alkoxy, (C<sub>1</sub>-C<sub>4</sub> alkyl)thio, halo, or R<sub>2</sub>-  
substituted phenyl;

each R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen,  
halo, hydroxy, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, (C<sub>1</sub>-C<sub>4</sub>  
20 alkyl)-S(O)<sub>q</sub>-, trifluoromethyl, or di-(C<sub>1</sub>-C<sub>3</sub>  
alkyl)amino;

X is -O-, -S-, -C(=O)-, or -CH<sub>2</sub>-;

25 Y is -O- or -CH<sub>2</sub>-;

or when taken together, -X-Y- is -CH=CH- or





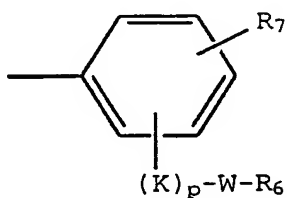
-39-

Z is a straight or branched chain C<sub>1</sub>-C<sub>10</sub> alkyldenylyl;

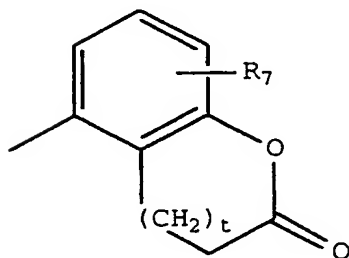
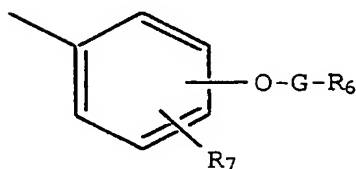
5

A is a bond, -O-, -S-, -CH=CH-, or -CR<sub>a</sub>R<sub>b</sub>-, where R<sub>a</sub> and R<sub>b</sub> are each independently hydrogen, C<sub>1</sub>-C<sub>5</sub> alkyl, or R<sub>7</sub>-substituted phenyl, or when taken together with the carbon atom to which they are attached form a C<sub>4</sub>-C<sub>8</sub> cycloalkyl ring;

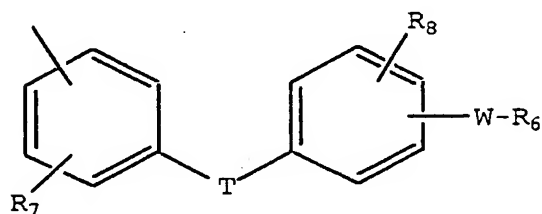
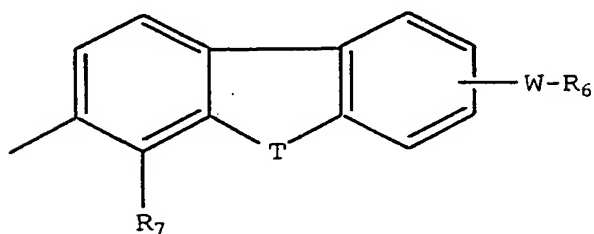
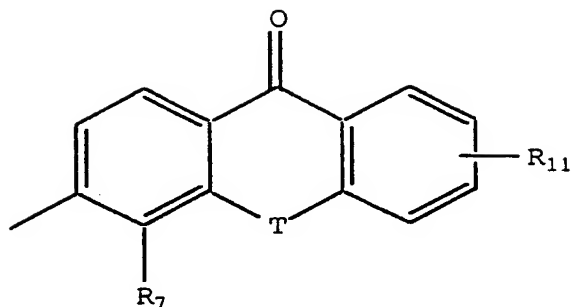
R<sub>4</sub> is R<sub>6</sub>



10



-40-



where,

5

each R<sub>6</sub> is independently -COOH, 5-tetrazolyl, -CON(R<sub>9</sub>)<sub>2</sub>, or -CONHSO<sub>2</sub>R<sub>10</sub>;

10

each R<sub>7</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>5</sub> alkenyl, C<sub>2</sub>-C<sub>5</sub> alkynyl, benzyl, methoxy, -W-R<sub>6</sub>, -T-G-R<sub>6</sub>, (C<sub>1</sub>-C<sub>4</sub> alkyl)-T-(C<sub>1</sub>-C<sub>4</sub> alkylidenyl)-O-, or hydroxy;

R<sub>8</sub> is hydrogen or halo;

-41-

each R<sub>9</sub> is independently hydrogen, phenyl, or C<sub>1</sub>-C<sub>4</sub> alkyl, or when taken together with the nitrogen atom form a morpholino, piperidino, piperazino, or pyrrolidino group;

5

R<sub>10</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl or phenyl;

R<sub>11</sub> is R<sub>2</sub>, -W-R<sub>6</sub>, or -T-G-R<sub>6</sub>;

10

each W is a bond or straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

15

each G is a straight or branched chain divalent hydrocarbyl radical of one to eight carbon atoms;

each T is a bond, -CH<sub>2</sub>-, -O-, -NH-, -NHCO-, -C(=O)-, or -S(O)<sub>q</sub>-;

20

K is -C(=O)- or -CH(OH)-;

each q is independently 0, 1, or 2;

p is 0 or 1; and

25

t is 0 or 1;

provided when X is -O- or -S-, Y is not -O-;

30

provided when A is -O- or -S-, R<sub>4</sub> is not R<sub>6</sub>;

provided when A is -O- or -S- and Z is a bond, Y is not -O-; and

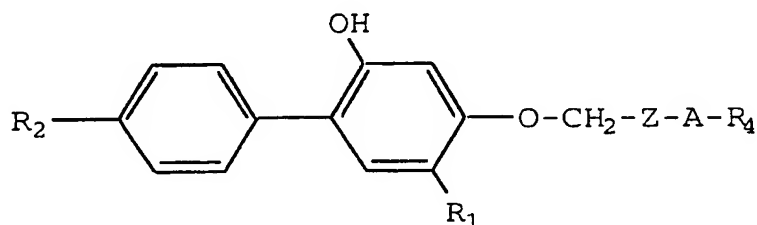
35

provided W is not a bond when p is 0;

-42-

or a pharmaceutically acceptable salt or solvate thereof,  
optionally in combination with a pharmaceutically acceptable  
excipient, for the preparation of a pharmaceutical  
composition for treating or inhibiting gingivitis in a  
5 mammal

10. The use according to **claim 9** employing a  
compound of the formula;



or a pharmaceutically acceptable salt or solvate thereof.

11. The use according to **claim 9** wherein the  
15 compound employed is 2-[2-propyl-3-[3-[2-ethyl-4-(4-  
fluorophenyl)-5-hydroxyphenoxy]propoxy]phenoxy]benzoic acid  
or a pharmaceutically acceptable salt or solvate thereof.

12. The use according to **claim 9** wherein the  
20 compound employed is 3-(2-(3-(2-ethyl-4-(4-fluorophenyl)-5-  
hydroxyphenoxy)propoxy)-6-(4-carboxy-  
phenoxy)phenyl)propionic acid or a pharmaceutically  
acceptable salt or solvate thereof.

13. The use according to **claim 9** wherein the  
25 compound employed is 1-(4-(carboxy-methoxy)phenyl)-1-(1H-  
tetrazol-5-yl)-6-(2-ethyl-4-(4-fluorophenyl)-5-  
hydroxyphenoxy)hexane or a pharmaceutically acceptable salt  
or solvate thereof.

-43-

14. The use according to **claim 9** wherein the compound employed is 3-[4-[7-carboxy-9-oxo-3-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]-9H-xanthene]]propanoic acid or a pharmaceutically acceptable  
5 salt or solvate thereof.

15. The use according to **claim 9** wherein the compound employed is 5-[3-[2-(1-carboxy)-ethyl]-4-[3-[2-ethyl-4-(4-fluorophenyl)-5-hydroxyphenoxy]-propoxy]phenyl]-  
10 4-pentynoic acid or a pharmaceutically acceptable salt or solvate thereof.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US98/05436

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/41, 31/52

US CL : 514/266, 381

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/266, 381

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE, MEDLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A, 9641645 (ANDERSON ET AL.) 05 FEBRUARY 1997, SEE ENTIRE DOCUMENT.	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*B* earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

28 MAY 1998

Date of mailing of the international search report

30 JUL 1998

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